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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,182	06/19/2002	William A. Banks	01017/36667	7965

4743 7590 10/13/2006

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,182	BANKS, WILLIAM A.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *6-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-77* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 7 August 2006 have been entered. Claim 77 is new; claims 1 – 77 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Claims 6 – 76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1 March 2005.

4. This application contains claims 6 – 76 drawn to an invention nonelected with traverse in the remarks filed 1 March 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Claims 1 – 5 and 77 are under examination.

Withdrawn Rejections and Objections

6. The following rejections and objections made in the previous office action are withdrawn:

A. The objection to claims 1 – 4 is withdrawn in light of the amendments.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 112

7. Claims 1 – 5 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased transport of leptin across the blood-brain barrier (BBB) following coadministration of leptin and an adrenergic agonist does not reasonably provide enablement for increased transport of leptin across the BBB following administration of leptin variants, analogs, fusion proteins, derivates or fragments as broadly defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons of record, as it pertains to making and using leptin fusion proteins, chemically modified derivatives, and fragments which are "biologically

active" as recited in claim 3, for example. Note that applicant's amendments are sufficient to overcome the other previously-stated grounds of rejection.

The claims as written encompass administration of leptin as well as fragments, derivatives, and fusion proteins. Leptin is a protein of 146 amino acids (specification, p. 9). The art of record indicates that very subtle changes to the leptin sequence, such as single amino acid substitutions, drastically alter the function of the molecule (see Peelman 2004., cited in office action mailed 31 March 2005). Furthermore, the art indicates that proteins which bind leptin can modulate leptin's transport across the blood-brain barrier (see Ramsey et al., submitted by applicant on IDS). The specification provides working examples of modulating the transport of leptin, but not of any fusion proteins, chemically modified derivatives, or fragments of leptin. The claims do not require that the leptin administered be able to pass through the blood-brain barrier, but only require that the protein be "biologically active". This term is not explicitly defined in the specification, and the broadest reasonable interpretation of the term includes simply retaining the ability to be bound by an antibody, or having the ability to dissolve in physiological saline.

What is enabled, increased transport of exogenous leptin after co-administration of leptin and epinephrine, is considerably narrower than what has been claimed. The specification recites certain particular modifications that one could make to leptin such that it would still be transported across the BBB, i.e. on p. 11 lines 17 – 27). However, there is not guidance as to what deletions or derivations one should make in order to retain "biological activity" as claimed. The lack of guidance in the specification as to how to ensure that a leptin fragment, derivative, or fusion protein is "biologically active" after such modification, combined with the teachings in the art which indicate that leptin is exquisitely sensitive to subtle mutations, and that its transport across the BBB can be altered if it binds to other molecules, indicates whether biologicala ctivity is retained is unpredictable. Given the lack of adequate guidance in the specification, the breadth of the claims, the existence of working examples which deal with leptin only and not with derivatives, fragments, or fusion proteins, and the lack of predictability in the art, the skilled artisan would have to resort to undue experimentation in order to make and use the starting materials required for the invention.

Applicant argues, on p. 13 of the remarks, that it would not take undue experimentation as "all of the leptins recited in the claims are enabled in the specification and in the art". Applicant cites several patents and sections of the specification in support of the argument.

While the cited patents do broadly discuss fragments and variants, etc., the instant claims are drawn to any fragment, or any derivative, which has biological activity. Note that the claims of both the cited patents in fact recite specific fragments and derivatives, in contrast to the instant claims, which are drawn to any fragment or derivative. Similarly, the instant specification teaches the artisan how to make certain fragments and hypothesizes that these might be useful in the instant invention. However, neither the prior art nor the instant specification teach the artisan how to make and use the full scope of the invention now claimed. What is claimed is broad, and what the prior art and specification enable are narrow by comparison.

8. Claims 1 – 5 and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection is maintained for the reasons of record, as it pertains to whether applicant was in possession of methods of using leptin fusion proteins, chemically modified derivatives, and fragments which are "biologically active" as recited in claim 3, for example. Note that applicant's amendments are sufficient to overcome the other previously-stated grounds of rejection.

Applicant is referred to the previous office actions for a more detailed explanation of why the claimed invention is not adequately described. See, for example, pp. 7 – 8 of the office action mailed 31 March 2005, pp. 7 – 8 of the office action mailed 18 August 2005. Applicant argues, on p. 15 of the instant remarks, that as the prior art teaches certain fragments of leptin which have specific activities, such as the ability to decrease body weight, the instant invention is adequately described. The examiner disagrees. The claims here are drawn to administration of any leptin, fusion protein, derivative, or fragment thereof, which has "biological activity". As stated above, this term is not limited in the specification to any particular activity, and thus reasonably encompasses anything "biological", such as the ability to be digested by proteases, or the ability to be recognized by an antibody. While those fragments of leptin which have been described in the prior art need not be described in the instant specification, the claims are much broader than the fairly limited prior art disclosures. The claims encompass an unlimited number of possible fragments with an unlimited number of possible activities. The skilled artisan cannot

visualize the full genus of molecules that are to be administered, and the specification does not set forth those structures which are common to all members of the genus. The invention that is claimed, administration of leptin or a fusion, fragment, or derivative thereof, has not been described because the genus is much broader than what is actually disclosed in the specification.

Claim Rejections - 35 USC § 103

9. Claims 1 – 5 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banks (1996, of record), in view of Borges (1994, of record) and Caro (1996, of record).

This rejection is maintained for the reasons of record. Briefly, Banks teaches that leptin enters the brain via a saturable transporter, Borges teaches that epinephrine modulates the exclusionary properties of the BBB, and Caro provides motivation to increase the amount of leptin entering the brain. As the teachings of the references have been described in detail in the previous office actions, they will not be repeated herein.

It would have been obvious to one of ordinary skill in the art to administer exogenous leptin and epinephrine in an amount effective to modulate transport of leptin across the BBB, with a reasonable expectation of success. The motivation to do so is to increase the amount of leptin that reaches the hypothalamus, thereby signaling satiety to obese patients. This motivation is provided by Caro. It would be reasonable to expect success, as Borges teaches that administration of epinephrine is sufficient to modulate transport of impermeable molecules across the BBB, and Banks teaches that leptin is an impermeable molecule because the transport system is saturable. Furthermore Borges provides guidance to select a dose of epinephrine (100 nM) which has been shown in the instant disclosure to be effective in modulating transport of leptin across the BBB through its specific transporter.

Applicant appears to acknowledge the examiner's argument, on p. 19 of the remarks. Applicant states "[o]ne of ordinary skill would reasonably expect, based on the teachings in the art, that administration of epinephrine would disrupt the BBB to such an extent that any molecule would diffuse across the BBB membrane". This is exactly the point; Borges teaches the artisan how to increase the permeability of the BBB, which is what Caro had pointed out as problematic and a possible cause of the lack of efficacy of exogenously-administered leptin. Applicant argues that it would be non-obvious "to look for a disclosure describing a specific BBB transport mechanism". Applicant is reminded that a different motivation for combining

references from applicant's is permissible; see MPEP § 2144. Here, the motivation to combine the references is to overcome the strict exclusionary properties of the BBB, which Caro states is the reason the leptin cannot enter the brain.

Applicant argues, on p. 17, that Caro argues exogenous leptin would be ineffective as it must be transported across the BBB. Caro teaches that the saturable transport mechanism may be rate-limiting, preventing leptin from entering the brain and thereby preventing the satiety signal that the peptide provides, leading to obesity. This would suggest to the artisan of ordinary skill that the transport mechanism is an obstacle to be overcome. Borges in fact provides an excellent solution to this problem. Borges teaches that administering epinephrine modulates the permeability of the BBB. See Borges, p. 245, Results and Figure 2. Borges provides guidance as to which doses are effective in modulating permeability; this includes doses that applicant also shows are effective in permitting transport of leptin across the BBB. Thus the artisan of ordinary skill, upon reading Banks, would be motivated to use the epinephrine (adrenaline) dosage disclosed therein to modulate BBB permeability. This would allow leptin to enter the brain, which Caro teaches is necessary for it to have its action in fighting obesity.

Applicant argues, on p. 18, that the reference by Sokrab (1988) teaches away from the claimed invention, as Sokrab teaches certain deleterious effects of the drug. While Sokrab does teach deleterious effects, the reference also teaches that the dose is effective in allowing proteins to enter cells within the brain. See Sokrab, p. 394. This provides further support for the examiner's contention that it would be obvious to co-administer leptin and epinephrine, particularly given the teachings of Caro. Sokrab also teaches that epinephrine is suitable to overcome the problem set forth by Caro, namely that leptin cannot enter the brain. While Sokrab does teach that there might be disadvantages to health in those who receive epinephrine, nothing in the reference actually teaches away from the invention. Nothing in Sokrab teaches that the doses used by Borges would not be effective in modulating BBB permeability.

Conclusion

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
September 18, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER